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**EDGEWOOD ARSENAL
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**TOXIGONIN AND PRALIDOXIME:
A KINETIC COMPARISON AFTER
INTRAVENOUS ADMINISTRATION TO MAN**

by

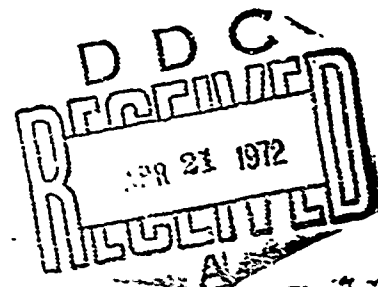
**Frederick R. Sidell
William A. Groff, Sr.
Andris Kaminskis**

March 1972



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**TOXOGONIN AND PRALIDOXIME: A KINETIC COMPARISON AFTER
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William A. Groff, Sr.
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Medical Research Division

March 1972

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Task 1W662710AD2501

**DEPARTMENT OF THE ARMY
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Edgewood Arsenal, Maryland 21010**

FOREWORD

The work described in this report was authorized under Task 1W662710AD2501, Medical Defense Against Chemical Agents, Biomedical Evaluation of Protective Materiel. This work was started in April and completed in May 1971.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25.

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DIGEST

After intravenous administration to humans, the chloride and methane sulfonate salts of pralidoxime were found to have identical pharmacokinetic characteristics. Toxogonin was found to have a much smaller volume of distribution and a lower renal clearance rate. These findings explain the fivefold difference in plasma concentrations after similar doses of toxogonin and pralidoxime.

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TOXOGONIN AND PRALIDOXIME: A KINETIC COMPARISON AFTER INTRAVENOUS ADMINISTRATION TO MAN

I. INTRODUCTION.

The pyridinium oximes are widely accepted as valuable adjuncts to atropine in the therapy of anticholinesterase intoxication. Pralidoxime chloride (2-pyridine aldoxime methochloride) is the preparation used in this country, and toxogonin [N,N'-oxydimethylenebis(pyridinium-4-aldoxime)dichloride] seems to be the preferred compound in Europe. The structures of the two compounds are basically similar, but toxogonin consists of two pyridinium rings linked by an oxygen molecule. Thus, it is about twice the size and weight of pralidoxime chloride.

Previous studies with pralidoxime chloride and toxogonin have shown a marked difference between these two closely related materials in the relationship of apparent dose and plasma concentration. When given orally, toxogonin produced plasma oxime concentrations about equivalent to those produced by the same doses of the single moiety salt.^{1,2} However, the urinary recovery of toxogonin was much less than the recovery of pralidoxime. Because most of the compound seems to be eliminated by this route, this suggests that the actual dose of toxogonin entering the body may be much smaller despite the equivalent plasma concentrations. After intramuscular administration of equal doses (by weight), the plasma concentrations of oxime were four to five times higher after toxogonin than after pralidoxime chloride, although urinary recoveries were similar.^{3,4}

These findings strongly suggest a difference in the volume of distribution for these compounds. To investigate this further, the two drugs and pralidoxime methane sulfonate were given intravenously to volunteer subjects.

Although in principle the meaning should be clear, the term "volume of distribution" has been defined in various ways.⁵ A brief review of these definitions and their interrelationships is a secondary purpose of this report.

II. EXPERIMENTATION.

A. Subjects.

The subjects were US Army enlisted men who volunteered to participate after the test was discussed with them. Each had a complete medical evaluation including a physical examination, chest X-ray, electrocardiogram, and laboratory tests [hematocrit, total and differential white blood cell count, urinalysis, blood urea nitrogen (BUN) serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin, creatinine, and red blood cell and plasma cholinesterase] and was found to be free from abnormality before he was accepted into the study.

¹Sidell, F. R., and Groff, W. A. Toxogonin: Oral Administration to Man. *J. Pharm. Sci.* 60, 860-863 (1971).

²Sidell, F. R., Groff, W. A., and Ellin, R. I. Blood Levels of Oxime and Symptoms in Humans after Single and Multiple Oral Doses of 2-Pyridine Aldoxime Methochloride. *J. Pharm. Sci.* 58, 1093-1098 (1969).

³Sidell, F. R., and Groff, W. A. Toxogonin: Blood Levels and Side Effects after Intramuscular Administration in Man. *J. Pharm. Sci.* 59, 793-797 (1970).

⁴Sidell, F. R., and Groff, W. A. Intramuscular and Intravenous Administration of Small Doses of 2-Pyridinium Methochloride to Man. *J. Pharm. Sci.* 60, 1224-1228 (1971).

⁵Wagner, J. G. Pharmacokinetics. In *Annual Review of Pharmacology*. Vol 8, pp 67-94. Annual Reviews, Inc., Palo Alto, California. 1968.

B. Methods.

The subjects were admitted to the test ward the evening before the test. The morning of the test they were given a light breakfast, and thereafter they were urged to drink large amounts of fluid to maintain a copious urinary output. The subjects who received pralidoxime chloride and pralidoxime methane sulfonate were asked to void at hourly intervals for the first 8 hours of the study; such a schedule was not asked of the subjects who received toxogonin.

Heart rate and blood pressure were measured before and at close intervals after drug administration. As the results did not differ from those previously reported after these compounds, they are not reported.

Plasma was collected at the times shown in figure 1; these samples and all urine specimens for 24 hours were analyzed for oxime content by methods described elsewhere.⁶ Each plasma and urine specimen was analyzed for creatinine content by standard methods.

Although they were permitted to be out of bed, most subjects remained in bed (except to void) for the first 3 hours.

Toxogonin, from the same lot described previously,³ was mixed to a concentration of 100 mg/ml. The pralidoximes were dissolved to the same concentration. Because there were data on the pralidoximes given intravenously,^{4,7} only one dose, 5 mg/kg, was given; two doses of toxogonin, 5 mg/kg (two subjects) and 1.0 mg/kg (three subjects), were given.

III. RESULTS.

A. Plasma Concentration.

Figure 1 shows the mean plasma concentrations for each of the four groups. The group receiving 1.0 mg/kg of toxogonin had a plasma concentration versus time curve very similar to those of the groups receiving 5.0 mg/kg of the pralidoximes.

B. Urinary Recovery and Renal Clearance.

Of the toxogonin administered, 68% ± 8%* was recovered in the urine within 24 hours. Recovery of pralidoxime chloride was 89.8% ± 2.6% and of pralidoxime methane sulfonate was 87.1% ± 20%. For the pralidoximes, about 50% of the total was recovered within the first hour and about 70% within the first 2 hours. Because the subjects receiving toxogonin did not follow a regular voiding schedule, comparable values are not available, but most of the recovered drug was found in their early specimens.

The renal clearance is usually defined as

$$Cl_x = \frac{U_x V}{C_{p_x}} \quad (1)$$

⁶Groff, W. A., and Ellin, R. I. A New and Rapid Method for the Determination of the Pyridinium Aldoximes in Blood and Urine. *Clin. Chem.* 15, 72 (1969).

⁷Sundwall, A. Plasma Concentration Curves of N-Methylpyridinium-2-aldoxime methane sulphonate (P2S) after Intravenous, Intramuscular and Oral Administration in Man. *Biochem. Pharmacol.* 5, 225-230 (1960).

*Mean ± SD.

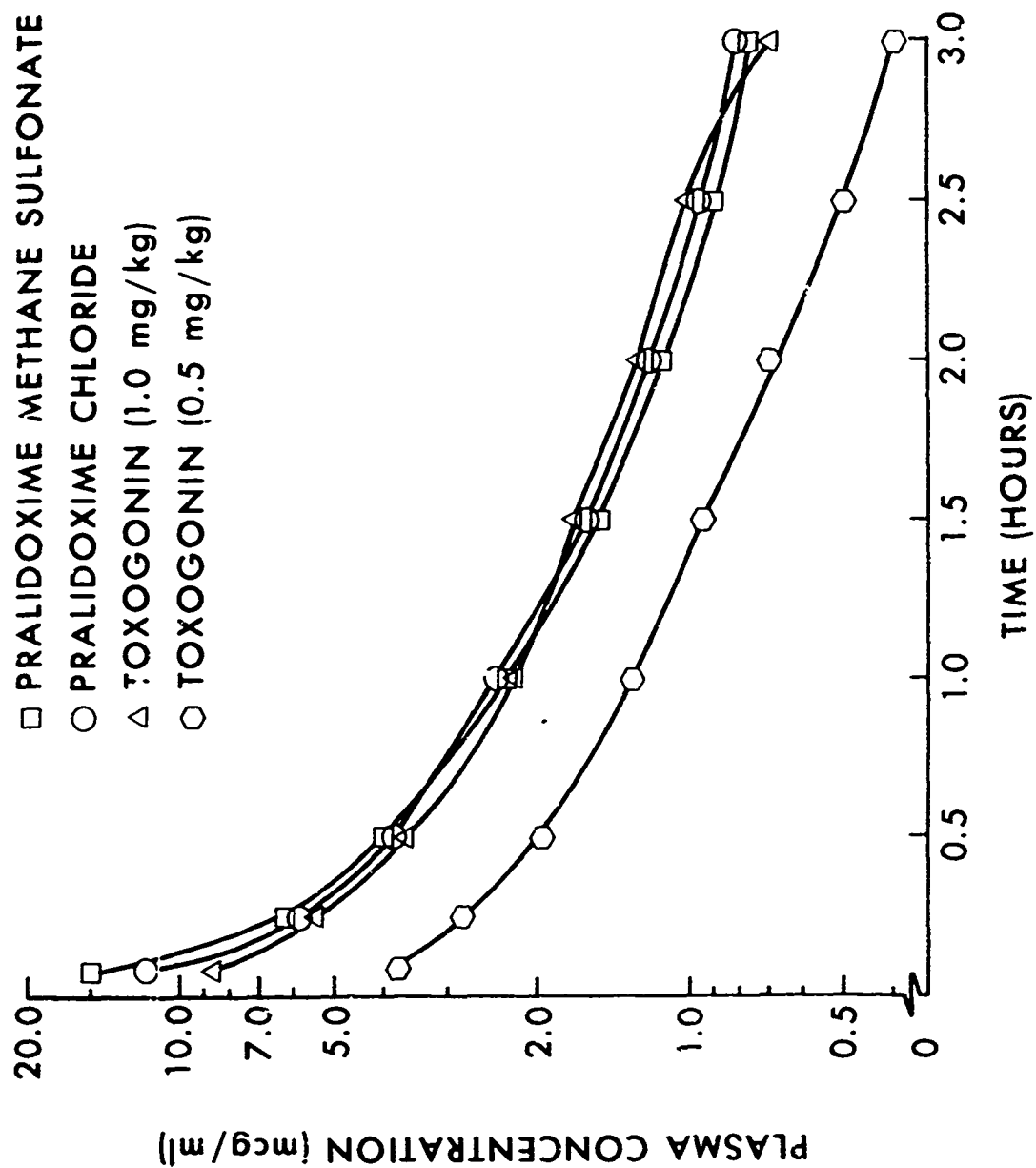


Figure 1. Pralidoxime Chloride, Pralidoxime Methane Sulfonate, and Toxogonin: Plasma Concentrations After Intravenous Administration to Humans

where

Cl_x = renal clearance of compound x

U_x = urinary concentration of x

C_{p_x} = plasma concentration of x at the midpoint of the collection interval

V = urinary volume per unit time

The renal clearance for each subject was calculated by this method using the plasma concentration estimated from the plasma concentration versus time plot. The mean clearances over the 3- to 6-hour period after drug administration are shown in table I.

When the plasma concentration is changing rapidly, as it frequently does after intravenous administration of a compound, the regression line of the plot of the rate of renal excretion (amount per unit time) versus the plasma concentration at the midpoint of the urinary collection interval is the renal clearance.⁸ These values are also shown in table I (in a few instances, an extremely high value that significantly changed the slope was omitted).

A third method is to use the ratio of the total amount excreted over the total area under the plasma concentration versus time plot.⁸ The advantages of this are that frequent, carefully timed urine specimens are unnecessary, and the only analysis of urinary drug content that is necessary is the one on the single cumulative sample. The accuracy of this method depends primarily on the accuracy with which the area can be estimated. This method also has a theoretical basis (see below). Clearances calculated by this method are shown in table I.

A slight modification of this is to use the mean of the incremental cumulative clearance (i.e., cumulative amount excreted to time = t_1, t_2, t_3 , etc., divided by the cumulative area under the curve to times t_1, t_2, t_3 , etc.). Kwan, Wadke, and Foltz⁹ indicated that fluctuations from one time period to the next (which presumably are a result of experimental error or physiological variations) are minimized by this method. The means of these values for each subject are shown in table I.

With several exceptions, the values for each subject are in good agreement. The disparity between the values based on the cumulative methods and the other two values for subject 3656 is undoubtedly because of the low excretion (see f , fraction of dose excreted, in table I), and we have reason to believe an early specimen was accidentally discarded.

The renal clearance of endogenous creatinine was measured simultaneously with the drug clearances (calculation was by the standard method). The pralidoxime clearance was about four times that of simultaneously measured endogenous creatinine clearance, whereas the rate of toxogonin clearance was less than that of creatinine. Thus, despite their structural similarities, these compounds appear to be handled differently by the kidneys. The net effect for the pralidoximes is one of tubular secretion while toxogonin appears to be reabsorbed. (Other studies in our laboratory have indicated that the compounds are not appreciably bound to plasma proteins.)

⁸Wagner, J. G. Pharmacokinetics. J. M. Richards Laboratory, Grosse Pointe Park, Michigan. 1969.

⁹Kwan, K. C., Wadke, D. A., and Foltz, E. L. Pharmacokinetics of Phosphonomycin in Man. I: Intravenous Administration. J. Pharm. Sci. 60, 678-685 (1971).

Table I. Renal and Plasma Clearances of Oximes

Compound and case No.	Dose	Wt	Renal clearance				Plasma clearance	f, Fraction of dose recovered in urine
			Standard ^a	Slope ^b	Cumulative ^c	24-Hr cumulative ^d		
	mg/kg	kg	ml/min					
Toxogonin								
3139	0.5	71	97 ±30 ^e	87	82	83	128	0.647
3140	0.5	71	91 ±6	82	77	83	137	0.595
3141	1.0	70	82 ±0.5	80	79	86	129	0.658
3142	1.0	70	118 ±14	110	104	123	151	0.811
3143	1.0	63.1	87 ±8	79	76	84	120	0.694
Mean			95	88	83	92	133	0.681
SD			14	13	12	17	12	0.081
Pralidoxime chloride								
3658	5.0	84.5	582 ±292	738	775	726	784.4	0.915
3655	5.0	71.8	620 ±224	679	679	662	733	0.911
3657	5.0	90.3	616 ±170	634	666	648	744.9	0.869
Mean			606	638	707	679	754	0.898
SD			21	44	60	42	27	0.026
Pralidoxime methane sulfonate								
3654	5.0	67.3	659 ±396	735	747	713	717.6	0.978
3659	5.0	78.2	603 ±521	587	748	700	685.4	1.00
3656	5.0	85.9	670 ±114	593	369	402	633.2	0.636
Mean			644	638	621	605	679	0.871
SD			36	84	219	176	46	0.204

^aFrom UV/P.^bFrom slope of rate of excretion versus plasma concentration.^cFrom mean of ratios of cumulative amount excreted to cumulative area under the plasma concentration versus time curve.^dThe ratio of the total amount excreted to the total area under the plasma concentration versus time curve.^eMean ± SD.

C. Kinetic Considerations.

1. General.

Using the method of residuals and a programmable calculator to obtain the best fitting monoexponential line, the constants A , α , B , and β^* were obtained for each subject. From these, the rate constants and volumes of distribution applicable to a two-compartment open model, k_{12} , k_{21} , k_{13} , V_1 , and V_2 , were calculated. These are shown in table II.

The half times for elimination from the plasma ($0.693/\beta$) are similar for all three compounds (1.20 hours for toxogonin, 1.41 hours for pralidoxime methane sulfonate, and 1.3 hours for the chloride).

2. Plasma Clearance.

For a two-compartment model, the plasma clearance (Cl_p) may be defined as:⁸

$$Cl_p = V_1 k_{13}, \text{ or} \quad (2)$$

$$Cl_p = \frac{D}{AUC} \quad (3)$$

where AUC is the area under the plasma concentration versus time curve, and D is the dose.

Using the integrated form of the equation for plasma concentration versus time to obtain the AUC , the Cl_p values were calculated and are shown in table I.

Because the renal clearance is equal to the plasma clearance multiplied by the fraction of the dose excreted in the urine (f), the ratio of renal clearance to plasma clearance should equal this fraction.⁸ This is actually true only with the renal clearance that is calculated from the total (24 hour) amount of drug excreted. The values for f are shown for each subject in table I.

3. Volume of Distribution.

The volume of distribution is the hypothetical volume in which the drug is present in the same concentration as it is in the plasma. Or, the volume of distribution (V_d) is the ratio of the amount of drug in the body (D_b) to the plasma concentration (C_p),

$$V_d = \frac{D_b}{C_p} \quad (4)$$

A basic assumption is that V_d is constant, and that this relationship should be true for all values of C_p (i.e., from $t = 0$ to $t = \infty$). If a drug behaved as though it were distributed in a single compartment, this would be valid concept. However, the distribution and excretion patterns of many drugs appear to follow two-compartment model kinetics. Under these circumstances, a single volume of distribution over the entire time course is not as easily defined.

After rapid intravenous administration of a drug, the concentration in the blood (which is part of the central compartment) usually falls rapidly for a period of time, followed by a more

*See appendix for definitions and derivations not described in the text.

Table II. Pharmacokinetic Constants

Compound and case No.*	A	α	B	β	$t_{1/2}$	k_{12}	k_{21}	k_{13}	V_1	V_2	$(V_d)_{ss}$	$(V_d)_\beta$
	mcg/ml	hr ⁻¹	mcg/ml	hr ⁻¹	hr	ml/kg						
Toxogonin												
3139	2.205	4.95	2.788	0.667	1.04	1.476	3.058	1.080	100.1	48.3	148.4	161.8
3140	2.340	3.58	1.914	0.522	1.33	1.224	1.896	0.984	117.5	75.9	193.4	222.0
3141	4.656	4.26	4.546	0.576	1.20	1.422	2.394	1.020	108.7	64.6	173.3	193.0
3142	10.129	5.57	3.954	0.667	1.04	2.442	2.070	1.824	71.0	83.8	154.8	194.5
3143	5.849	3.56	3.60	0.498	1.39	1.560	1.818	1.080	105.8	90.8	196.6	230.5
Mean		4.48		0.586	1.20	1.625	2.247	1.198	100.6	72.7	173.3	200.4
SD		0.83		0.079	0.16	0.473	0.504	0.353	17.7	16.7	21.8	27.2
Pralidoxime chloride												
3658	12.456	6.65	3.68	0.518	1.34	3.454	1.916	1.789	309.9	558.6	868.5	1075
3655	17.120	6.43	2.66	0.484	1.43	3.199	1.282	2.423	252.78	630.5	883.3	1266
3657	15.24	8.10	4.85	0.590	1.17	4.298	2.403	1.989	248.9	445.15	694.0	839
Mean	14.94	7.06	3.73	0.531	1.31	3.650	1.867	2.070	270.5	544.8	815.2	1060
SD	2.35	0.91	1.10	0.05	0.13	0.575	0.562	0.320	34.1	93.4	105.3	214
Pralidoxime methane sulfonate												
3654	18.776	6.72	2.34	0.466	1.49	3.325	1.159	2.702	236.8	678.5	915.2	1373
3659	25.04	8.74	2.87	0.432	1.60	4.950	1.286	2.936	179.5	689.6	868.7	1218
3656	23.90	7.69	5.0	0.610	1.14	3.909	1.835	2.559	173.0	368.6	541.6	725
Mean	22.57	7.717	3.40	0.503	1.41	4.061	1.427	2.732	196.3	578.6	775.2	1105
SD	3.34	1.01	1.41	0.09	0.24	0.823	0.359	0.190	35.2	182.5	204.0	338

^aSee table I for doses.

gradual decline. The concentration is highest immediately after the injection (or at zero time). The concentration in the tissue (or peripheral) compartment is zero at zero time. The tissue concentration increases to a maximum, and then declines in parallel with the plasma concentration (the "β phase," see appendix). As the plasma and tissue concentrations maintain a constant relationship during the β phase, a single volume of distribution [designated as $(V_d)_\beta$, which is equivalent to $(V_d)_{area}$; see appendix] can relate the amount of drug in the body to the plasma concentration during this period.¹⁰ But the relationship does not hold for the earlier period.

The steady state volume of distribution, $(V_d)_{ss}$, is the ratio of the amount of drug in the body to the plasma concentration at steady state conditions; i.e., when rate of drug transfer into the peripheral compartment is equal to the rate of transfer back to the central compartment.¹¹ This is a momentary phenomenon, and only at this instant does $(V_d)_{ss}$ relate amount of drug in the body to the plasma concentration.

Using separate volumes for each compartment, the amount of drug in the body is defined by

$$D_b = C_p \cdot V_1 + C_t \cdot V_2 \quad (5)$$

where

V_1 = the volume of the central compartment

V_2 = the volume of the peripheral compartment

C_t = the tissue concentration

Because this expression accounts for the amount of drug in the body over all time periods and the similar expression using $(V_d)_\beta$ does not (see appendix), equation (5) would seem to be more appropriate.

Because it can be shown (see appendix) that

$$(V_d)_{ss} = V_1 + V_2 \quad (6)$$

it would appear that $(V_d)_{ss}$ is a more appropriate single expression of V_d than $(V_d)_\beta$ [or the equivalent $(V_d)_{area}$], despite its inapplicability over most time periods.

There is also experimental evidence suggesting that $(V_d)_{ss}$ may be the preferred value. Wagner, Aghajanian, and Bing¹⁰ showed that the calculated tissue concentration of LSD paralleled scores on a performance test (which they assumed was a direct reflection of tissue concentration) over all time periods. Their calculations were based on a two-compartment model with $V_d = V_1 + V_2$. Sidell and Groff⁴ used the two-compartment model to estimate the amount of drug remaining in the body at all times after intravenous 2-PAMCl. This mathematical expression was verified by material balance experiments in man.

¹⁰Wagner, J. G., Aghajanian, G. K., and Bing, O. H. L. Correlation of Performance Test Scores with "Tissue Concentration" of Lysergic Acid Diethylamide in Human Subjects. Clin. Pharmacol. Ther. 9, 635-638 (1969).

¹¹Gibaldi, M., Nagashima, R., and Levy, G. Relationship Between Drug Concentration in Plasma or Serum and Amount of Drug in Body. J. Pharm. Sci. 58, 193-197 (1969).

A similar calculation can be made using the present data. The amount in the body (D_b), from $t = 0$ to $t = \infty$, over the time is⁴

$$D_b = \frac{D}{A\beta + B\alpha} [A\beta e^{-\alpha t} + B\alpha e^{-\beta t}] \quad (7)$$

If the entire dose were eliminated in the urine, the dose less the amount in the body should equal the amount excreted. Because urinary recovery is often less than 100%, the calculated amount excreted must be adjusted by this factor. This was done, and the results with experimental data for one subject are shown along with the mean data points for one drug group in figure 2. The experimental data (amount excreted) agree with the calculated line in each case.

Table II gives the values for V_1 , V_2 , $(V_d)_{ss}$, and $(V_d)_\beta$ [which equals $(V_d)_{area}$] for each subject.

The volumes for the pralidoxime salts do not differ notably from salt to salt, and both are considerably larger than the volumes for toxogonin. Generally, the overall volumes [whether $(V_d)_{ss}$ or $(V_d)_\beta$] are about five times greater for the pralidoximes than for toxogonin. The fivefold difference in volume relates to a fivefold difference in the dose of toxogonin needed to produce similar plasma levels of oxime.

IV. DISCUSSION.

The previously reported data that toxogonin produces higher plasma concentrations of oxime than equal doses of pralidoxime chloride can be attributed to the smaller volume of distribution of the former compound. The reason that toxogonin is not distributed as widely throughout the body as pralidoxime remains to be explained.

Comparative data on the therapeutic efficacy of the two oximes (summarized by Sidell and Gorff²) indicate that, at equimolar doses, toxogonin is several times more effective in treating animals poisoned with anticholinesterases. The plasma oxime concentrations were not measured in these studies, but it can be assumed that after equal doses, the plasma concentration of toxogonin would be higher than the plasma concentration of pralidoxime. Perhaps the suggested therapeutic advantage of toxogonin may not be caused by an inherent difference in potency per molecule, but rather by the higher concentration of oxime after toxogonin.

The two-compartment open model appears adequate to describe the pharmacokinetics of these compounds in man. Constants derived from data from one compartment (plasma) were used in equations derived on a theoretical basis from the model and predicted in a reasonable manner the observed values independently measured in another compartment (urine).

The definitions of volume of distribution and the various notations for this term were reviewed. Several that usually are designated by different symbolism were shown to be the same. In the interest of clarity, the symbols should be standardized and the equivalencies recognized.

Finally, renal clearances of these compounds were estimated using several commonly described methods. The values were not equal, but in most cases were in reasonably close agreement. If clearance is to be measured after a single injection of a drug, from a practical viewpoint the ratio of the total amount of drug excreted to the total area under the plasma concentration versus time curve has the advantage of eliminating the need for multiple, exactly timed urine specimens.

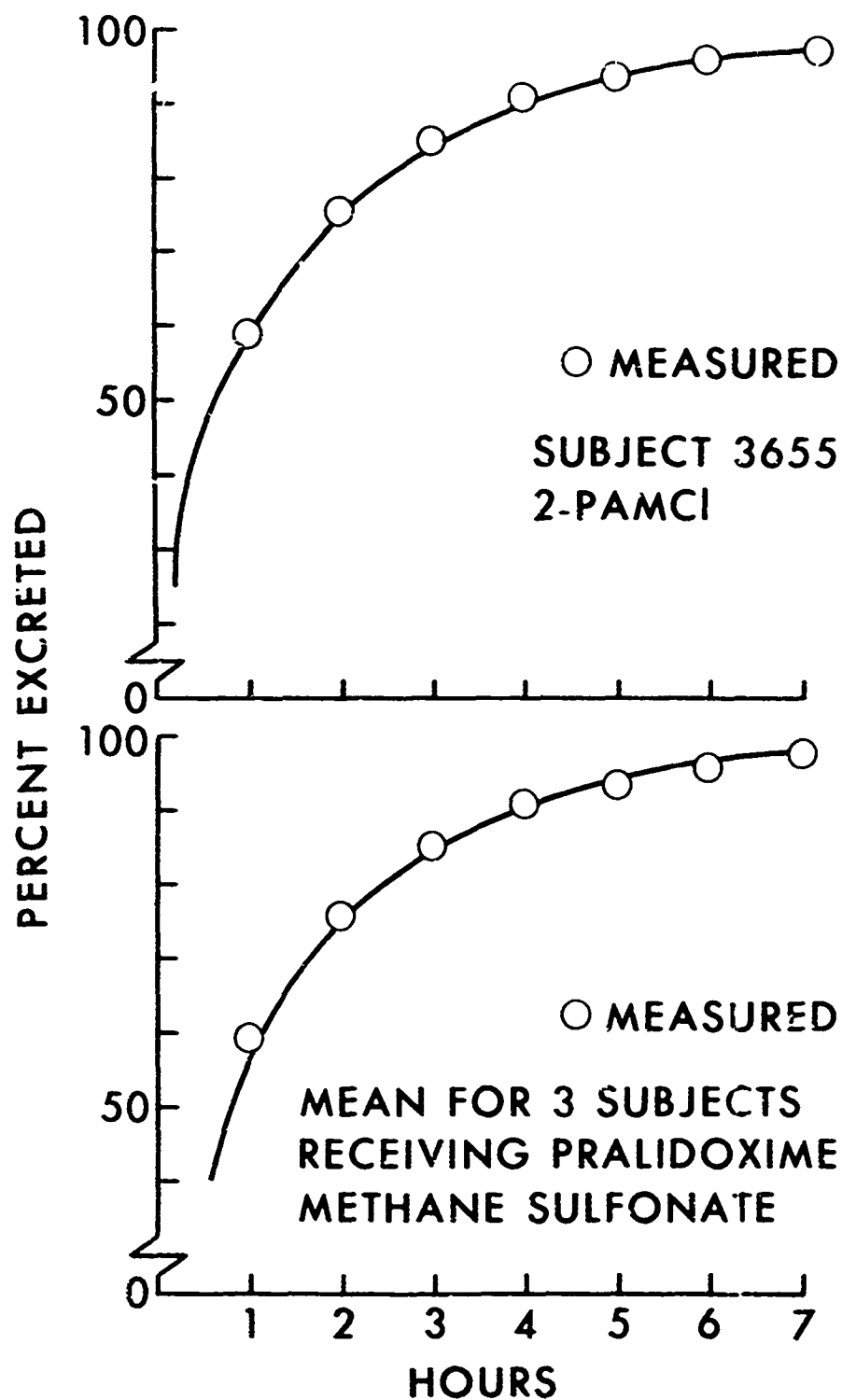


Figure 2. Pralidoxime Chloride and Pralidoxime Methane Sulfonate: Calculated and Experimental Urinary Excretion Values

V. SUMMARY.

After intravenous administration to humans, the chloride and methane sulfonate salts of pralidoxime were found to have identical pharmacokinetic characteristics. Toxogonin was found to have a much smaller volume of distribution and a lower renal clearance rate. These findings explain the fivefold difference in plasma concentrations after similar doses of toxogonin and pralidoxime.

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APPENDIX

DEFINITIONS AND DERIVATIONS

1. DEFINITIONS.

After intravenous administration of a compound, the relationship of the plasma concentration, C_p , to time, t , often is defined by

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1a)$$

where

β = -2.303 times the slope of the terminal linear segment (when the plasma level is displayed logarithmically against time on a linear scale)

B = the extrapolated zero-time intercept of this line

α = -2.303 times the slope of a line plotted by the method of residuals from the data points and β line

A = the zero-time intercept of the α line

The first-order rate constant describing the rate of drug transfer from the central to peripheral compartments is k_{12} ; the first-order rate constant for elimination of the drug (which is assumed to be from the central compartment) is k_{13} , and the first-order rate constant for transfer from the peripheral to central compartments is k_{21} .

In the two-compartment model, V_1 is the volume of the central compartment, V_2 is the volume of the tissue (or peripheral) compartment, and C_t is the drug concentration in the tissue compartment.

The values for these constants and C_t have been mathematically defined as follows:*

$$k_{21} = \frac{A\beta + B\alpha}{A + B} \quad (2a)$$

$$k_{13} = \frac{\alpha\beta}{k_{21}} \quad (3a)$$

$$k_{12} = \alpha + \beta - k_{13} - k_{21} \quad (4a)$$

$$V_1 = \frac{D}{A + B} \quad (5a)$$

*Wagner, J. G. Pharmacokinetics. J. M. Richards Laboratory, Grosse Pointe, Michigan. 1969.

$$V_2 = \frac{k_{12}}{k_{21}} \cdot V_1 \quad (6a)$$

$$C_t = \frac{k_{12} \cdot D}{(\alpha - \beta)(V_2)} (e^{-\beta t} - e^{-\alpha t}) \quad (7a)$$

By substitutions and rearrangement, these can be expressed in terms of the graphically defined A , α , B , and β as follows:

$$k_{13} = \frac{\alpha\beta(A+B)}{A\beta+B\alpha} \quad (8a)$$

$$k_{12} = \frac{AB(\alpha-\beta)^2}{(A+B)(A\beta+B\alpha)} \quad (9a)$$

$$V_2 = \frac{D}{A+B} \frac{AB(\alpha-\beta)^2}{(A\beta+B\alpha)^2} \quad (10a)$$

$$C_t = \frac{A\beta+B\alpha}{\alpha-\beta} \cdot e^{-\beta t} - e^{-\alpha t} \quad (11a)$$

II. EQUIVALENCY OF $(V_d)_\beta$ AND $(V_d)_{area}$

It has been stated* that

$$(V_d)_\beta = \frac{V_1}{f_c} \quad (12a)$$

where

f_c is the fraction of the amount of drug in the body that is in the central compartment, or

$$f_c = \frac{C_2}{C_2 + C_2'} \quad (13a)$$

where

$$C_2 = \frac{B}{A+B} \quad (14a)$$

and

$$C_2' = \frac{k_{12}}{(\alpha-\beta)} \quad (15a)$$

By substitution and rearrangement,

$$(V_d)_\beta = \frac{\alpha D}{A\beta+B\alpha} \quad (16a)$$

*Gibaldi, M., Nagashima, R., and Levy, G. Relationship Between Drug Concentration in Plasma or Serum and Amount of Drug in Body. J. Pharm. Sci. 58, 193-197 (1969).

Since*

$$(V_d)_{area} = \frac{D}{\beta(AUC)} \quad (17a)$$

$$(V_d)_{area} = \frac{\alpha D}{A\beta + B\alpha} = (V_d)_\beta \quad (18a)$$

III. EQUIVALENCY OF $(V_d)_{ss}$ AND $(V_1 + V_2)$.

$(V_d)_{ss}$ has been defined** as

$$(V_d)_{ss} = \frac{k_{21} + k_{12}}{k_{21}} \cdot V_1 \quad (19a)$$

By substitution from above and rearrangement,

$$(V_d)_{ss} = \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} \quad (20a)$$

Also by substitution from above,

$$(V_1 + V_2) = \frac{D}{A+B} + \left[\frac{D}{A+B} \right] \cdot \left[\frac{AB(\alpha - \beta)^2}{(A\beta + B\alpha)^2} \right] \quad (21a)$$

$$= \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} = (V_d)_{ss} \quad (22a)$$

IV. COMPARISON OF $(V_d)_\beta$ AND $(V_1 + V_2)$.

The amount of drug in the body should be the volume of distribution times the plasma concentration. Using $(V_d)_\beta$, this is

$$D_b = (V_d)_\beta \times C_p \quad (23a)$$

or

$$D_b = \frac{\alpha D}{A\beta + B\alpha} (Ae^{-\alpha t} + Be^{-\beta t}) \quad (24a)$$

During the β phase (when $e^{-\alpha t}$ is negligible), this becomes

$$D_b = \frac{\alpha D B e^{-\beta t}}{A\beta + B\alpha} \quad (25a)$$

**Ibid.*

***Ibid.*

and at $t = 0$, this becomes

$$D_b = \frac{\alpha D(A + B)}{A\beta + B\alpha} \quad (26a)$$

Using the two volumes of distribution,

$$D_b = C_p \cdot V_1 + C_t \cdot V_2 \quad (27a)$$

or

$$D_b = \frac{D}{A\beta + B\alpha} (A\beta e^{-\alpha t} + B\alpha e^{-\beta t}) \quad (28a)$$

During the β phase this becomes

$$D_b = \frac{\alpha D B e^{-\beta t}}{A\beta + B\alpha} \quad (29a)$$

which is the same as above. However, at $t = 0$, this becomes

$$D_b = D \quad (30a)$$

which is obviously the correct relationship for this time period.

V. RELATIONSHIP BETWEEN (V_d) AND $(V_d)_{ss}$

Since

$$(V_d)_\beta = \frac{\alpha D}{A\beta + B\alpha} \quad (31a)$$

and

$$(V_d)_{ss} = \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} \quad (32a)$$

$$(V_d)_\beta = \frac{\alpha(A\beta + B\alpha)}{A\beta^2 + B\alpha^2} \cdot (V_d)_{ss} \quad (33a)$$